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Mouse disabled (mDab1): a Src binding protein implicated in neuronal development.

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Here, we identify a mouse homolog of the Drosophila Disabled (Dab) protein, mDab1, and show it is an adaptor molecule functioning in neural development. We find that mDab1 is expressed in certain neuronal and hematopoietic cell lines, and is localized to the growing nerves of embryonic mice. During mouse embryogenesis, mDab1 is tyrosine phosphorylated wher the nervous system is undergoing dramatic expansion. However, when nerve tracts are established, mDab1 lacks detectable phosphotyrosine. Tyrosine-phosphorylated mDab1 associates with the SH2 domains of Src, Fyn and Abl. An interaction between mDab1 and Src is observed when P19 embryonal carcinoma (EC) cells undergo differentiation into neuronal cell types. mDab1 can also form complexes with cellular phosphotyrosyl proteins through a domain that is related to the phosphotyrosine binding (PTB) domains of the Shc family of adaptor proteins. The mDab1 PTB domain binds to phosphotyrosine-containing proteins of 200, 120 and 40 kDa from extracts of embryonic mouse heads. The properties of mDab1 and genetic analysis of Dab in Drosophila suggest that these molecules function in key signal transduction pathways involved in the formation of neural networks.

PMID: 9009273 [PubMed - indexed for MEDLINE]

1: Biochem J. 2004 Nov 15;384(Pt 1):1-8. Related Articles, Link
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Regulation of actin cytoskeleton by mDab1 through N-WASP and ubiquitination of mDab1.

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Migration of cells is critical to development of the central nervous system. Reelin, which was identified from the reeler mutant mice having a defect in the multilamellar structure of the brain, is thought to be a key signalling molecule that functions as a cue for determination of cell position. mDab1 (mouse Disabled homologue 1) functions downstream of Reelin. However, the mechanism by which mDab1 regulates cell migration during brain development is unknown. In the present paper, we show that mDab1 associates with N-WASP (neuronal Wiskott-Aldrich syndrome protein) in vitro and in brains of embryonic mice. mDab1 activates N-WASP directly, and induces actin polymerization through the Arp2/3 (actin-related protein 2/3) complex. mDab1 induces formation of filopodia when it is overexpressed in COS-7 cells. This filopodium formation is dependent on N-WASP, because expression of an N-WASP mutant that cannot induce Arp2/3-complex-mediated actin polymerization suppressed filopodium formation. The PTB (phosphotyrosine-binding) domain of mDab1 binds to N-WASP via the NRFY (Asn-Arg-Phe-Tyr) sequence close to the CRIB (Cdc42/Rac-interactive binding) motif of N-WASP and activates N-WASP in vitro. When mDab1 is phosphorylated by Fyn kinase in COS-7 cells, mDab1 is ubiquitinated in a Cbl-dependent manner, and mDab1 does not induce filopodium in the presence of activated Fyn. These findings suggest that mDab1 regulates the actin cytoskeleton through N-WASP, which is negatively regulated by phosphorylation-mediated ubiquitination of mDab1.

PMID: 15361067 [PubMed - in process]